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Health-related quality of life in long COVID-19 in context of symptom type

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Abstract

Aim: Coronavirus disease 2019 (COVID-19) is complex multisystem disease. After 4 weeks of persistent symptoms, it is termed as Long COVID-19. Long COVID-19 causes a decrease in health-related quality of life (HRQoL). In this study, it was aimed to determine which symptoms were associated with lower HRQoL in Long COVID-19 in this study.

Material and Methods: This cross-sectional study was conducted in a tertiary research hospital. Patients who have positive RT-PCR results at least 28 days and at most 180 days ago were selected for the study. Online survey was applied to 266 patients who had positive PCR test results for COVID-19. The EuroQoL 5D-3L scale was used to measure the HRQoL as a dependent variable. Socio-demographic features and symptoms were assessed by the survey as independent variables. Due to heteroscedasticity, a robust standard error regression analysis was conducted to make inferences on the effects of persistent symptoms on HRQoL.

Results: Of the total 266 participants, 163 were females (63.3%). The mean age was 41.2 ± 11.8 years. One hundred forty-two patients (53.3%) did not report any ongoing symptom . Female gender and lower education level as socio-demographic variables, visual problems and myalgia as persistent symptoms were identified as risk factors for reduced HRQoL in Long COVID-19 patients.

Discussion: Long COVID-19 patients experience lower levels of HRQoL, especially those with visual problems and/or myalgia. Interventions to raise the HRQoL of Long COVID-19 patients should first target visual problems and myalgia.

Keywords

COVID-19, Long COVID, HRQOL, Symptom Assessment, Regression Analysis

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Introduction

SARS-CoV-2 coronavirus (severe acute respiratory syndrome coronavirus 2), which is a pathogen of COVID-19 (coronavirus disease 2019), has infected over 535 million people and caused more than 6.5 million deaths globally, as of 17 June 2022 (available at: https://covid19.who.int/). Although it was seen as a respiratory disease at first, the complex multisystem nature of COVID-19 is well understood now [1]. COVID-19 can affect not only the lungs, but also the heart, coagulation system, kidney, brain and musculoskeletal system. Thus, it has various symptoms such as fatigue, headache, dizziness, anosmia, loss of taste etc.

Recently, while the rate of new cases of COVID-19 has declined sharply, Long COVID-19 is gaining more attention as a new phenomenon. Long COVID-19 is described as the occurrence of persistent symptoms after COVID-19 that cannot be explained better by another medical condition. In the presence of persistent symptoms, at least 4 weeks must pass from COVID-19 to accept that the patient has long COVID-19 [2]. But 4 weeks is not a definitive criterion according to the literature as even a period of more than 12 weeks after COVID-19 is also defined as Long COVID-19 in a report [3]. The pathophysiological basis of persistent symptoms after COVID-19 is not well understood, but it was shown that immunologic dysfunction plays a major role in this situation [4]. Progression from acute COVID-19 to Long COVID-19 is also independent of hospitalization needs at the acute COVID-19 stage [5]. The percentage of patients progressing to Long COVID-19 was determined as 2.3% to 60% [6,7]. The wide range between these presented percentages is probably due to the selection of patients with different durations after COVID-19.

Long COVID-19 causes a decrease in health-related quality of life (HRQoL) in the same way as COVID-19 [8,9]. Female gender and intensive care unit (ICU) admissions at the acute stage were determined as risk factors for reduction in HRQoL of patients who have Long COVID-19 [10,11]. But symptoms of Long COVID-19 were understudied in the context of lowering the effect on HRQoL. Fatigue has a significant effect on the lowering HRQoL, while dyspnea and anosmia have no effect on HRQoL according to a meta-analysis [11]. Hyposmia has also been shown to significantly reduce HRQoL in patients that suffer from Long COVID-19 [12]. Taboada at al. showed that dyspnea on exertion, myalgia, asthenia and arthralgia are associated with a decrease in HRQoL of Long COVID-19 patients, while insomnia, cough, anosmia and chest pain are not [13]. But these results depend on univariate statistics rather than multiple statistics (the type of statistics was not mentioned in the manuscript) that may lead to a raise in the type 1 error. Also, in the mentioned study, only patients who were admitted to ICU were sampled, so the generalizability of the study is limited.

Further research is needed to evaluate the HRQoL of Long COVID-19 patients by multiple statistics in the context of persistent symptoms. Thus, we aimed to determine which symptoms were associated with lower HRQoL in Long COVID-19.

Material and Methods

Study Design and Participants

This cross-sectional study was conducted in a tertiary research hospital in February 2022. Retrospective electronic health records of patients, who admitted to the outpatient clinic for COVID-19, were evaluated. People with positive reverse transcriptase polymerase chain reaction (RT-PCR) test results for COVID-19 were determined from a database of the hospital. Long COVID-19 has been described as ≥4 weeks after a positive RT-PCR [2]. Also due to the possible bias that may arise due to a novel phenomenon, patients with positive test results more than 180 days ago were not recruited in the study. To discriminate Long COVID-19 patients who have positive RT-PCR results at least 28 days and at most 180 days ago were selected as the study samples.

At first, 600 patients had positive RT-PCR for COVID-19. The number of patients who tested positive between ≥28 days and ≤180 days before was 320. We reached these 320 patients to obtain informed consent by telephone. Of these 320 patients, 24 did not give informed consent. Then, online links for the survey were sent to these 296 patients. However, 30 patients did not complete the survey. Thus, this study was conducted on 266 patients.

It was planned to use 22 independent variables for the multiple regression analysis for the study. When the minimum sample size was calculated according to the literature, it was shown that (20+5x22) 130 participants were sufficient [14]. Thus, in this study, more than double of the minimum number of patients were recruited.

Variables

HRQoL was defined as a continuous dependent variable. HRQoL of patients was measured by the EuroQoL 5D-3L scale [15]. The EQ-5D-3L1 is a widely used generic measure of health status consisting of two parts. The first part (the descriptive system) assesses health in five dimensions (Mobility, Self-care, Usual Activities, Pain/Discomfort, Anxiety/Depression), each of which has three levels of response (no problems, some problems, extreme problems/unable to). This part of the EQ-5D questionnaire provides a descriptive profile that can be used to generate a health state profile. For example, a patient with health status 11223 would have no problems in mobility and self-care, some problems with usual activities, moderate pain/discomfort, and extreme anxiety or depression. Each health state can potentially be assigned a summary index score based on societal preference weights for the health state. These weights, or utilities, are often used to compute Quality-adjusted life years (QALYs) for use in health economic analyses. Health state index scores generally range from less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than death) to 1 (perfect health), with higher scores indicating higher health utility, though health state preferences can differ between countries. The second part of the questionnaire consists of the Visual Analogue Scale (VAS), on which the patient rates his/her perceived health from 0 (the worst imaginable health) to 100 (the best imaginable health). The EQ-5D questionnaire is cognitively undemanding, taking

only a few minutes to complete. Instructions to patients are included in the questionnaire. For calculating the index score of the scale for each patient, the value set for our country is needed. However, there is no value for our country. So, in this study we used the value set of the United Kingdom, published by Dolan [16] as suggested in EuroQoL user guide (available at: https://euroqol.org/wp-content/uploads/2018/12/EQ-5D-3L-User-Guide_version-6.0.pdf).

Turkish validity and reliability of the scale were performed by the EuroQol Group [17] and the scale was obtained with the permission of the EuroQol Group under the registration number 50370.

The independent variables were collected via a survey that consist of socio-demographic questions and symptoms that started at the acute stage of COVID-19 and continued until the time of completion of the questionnaire. Participants had choices of "never or ceased" "yes and I still suffer" for each question of symptoms. These symptoms were headache, fatigue, dyspnea, hyposmia, loss of taste, dizziness, numbness in extremities, asthenia, myalgia, visual problems, hearing loss, hypokinesia, tremor, insomnia, pre-syncope/syncope, amnesia, difficulty in concentrate, anxiety, and sense of worthlessness.

Statistical analysis

Categoric variables were represented as frequencies and continuous variables were represented as mean ± standard deviation. If a continuous variable was not normally distributed, it was represented as median (25th percentile – 75th percentile). The linear relationships between variables were controlled by scatter dot plots.

First, univariate analysis (t-test with "not assumed equal variances") was conducted to see if patients who have specific symptom had a statistically significant difference in HRQoL compared to patients who did not have the symptom. Then Multiple linear regression was used as the main analysis to reduce Type 1 error. The Variance Inflation Factors (VIF) values for each independent variable were controlled, and if the VIF value was smaller than 10, then it was accepted as the absence of multicollinearity [18]. As most of our independent variables were categorical, it would be good to mention that it is appropriate to use dichotomous variables as independent variables in multiple linear regression [19]. After the multiple linear regression, the scatter plot of residuals vs predicted values was evaluated to see if the pre-test assumptions of the linear regression were satisfied. Heteroscedasticity was observed in the scatter-dot plot of the residuals. For dealing with the heteroscedasticity in regression analysis, "heteroscedasticity consistent standard errors" approach was needed, so, a general linear model was performed to reach HC3 version of the robust standard errors as suggested in the literature [20]. Reporting R-squared for robust regression is somehow controversial, but as it is not affected by heteroscedasticity [21], we chose to report the R-squared value obtained from multiple linear regression with the method of ordinary least squares to make a sense of percentage of explained variance of HRQoL by persistent symptoms. F statistic for the robust model was not reported because F statistics are biased by heteroscedasticity, and with robust standard error regression it no longer makes sense.

In the presence of missed variables, it was planned to exclude the missed case for concerning analysis. P-value lower than 0.05 was accepted as threshold for significance. All analyses were performed on IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.

Ethical Approval and Informed Consent

The study was approved by Çanakkale Onsekiz Mart University's Clinical Research Ethics Committee with ID of 2022-03. Verbal informed consent was taken from patients prior to the application of the online survey.

Results

Of a total of 266 participants, 163 were females (63.3%) and 103 (37.7%) were males. The mean age was 41.2 ± 11.8 years. The average duration elapsed from the positive RT-PCR test result was 103.9 ± 44.2 days. Of the participants, 12 (4.5%) did not need to take any medicine, 238 (89.5%) were treated at home, and 16 (6.0%) needed hospitalization at the acute stage of COVID-19. The number of participants who did not report any ongoing symptoms was 142 (53.3%). The most frequent symptoms were amnesia (20.7%) and fatigue (19.9%), respectively. The frequency of all persistent symptoms of the patients are shown in Table 1.

The EuroQoL 5D-3L index score ranged from 0.550 to 1.000, and its median was 1.000 (0.796 – 1.000). This High negative skewness of EuroQoL 5D-3L score occurred due to 182 (68.4%) participants reporting overall health state as 1.000. For the same reason, EuroQoL-VAS score of the patients was negatively skewed and its median was 100 (75-100).

Univariate analysis showed that all specified symptoms, except for the loss of taste and hearing loss, were associated with lower levels of HRQoL (Table 2). A robust standard error regression was calculated to make inferences about how various types of symptoms affect HRQoL in Long COVID-19. The dependent variable was HRQoL(EQ-5D-3L score), while

Table 1. Frequencies of persistent symptoms.

Symptom	Number Of Patients	Percentage (%)
Headache	18	6.8
Fatigue	53	19.9
Dyspnea	26	9.8
Hyposmia	29	10.9
Loss of Taste	19	7.1
Dizziness	16	6.0
Numbness on Extremities	13	4.9
Asthenia	38	14.3
Myalgia	35	13.2
Visual Problems	9	3.4
Hearing Loss	4	1.5
Hypokinesia	24	9.0
Tremor	8	3.0
Insomnia	24	9.0
Pre-syncope / Syncope	1	0.4
Amnesia	55	20.7
Difficulty in Concentrate	37	13.9
Anxiety	41	15.4
Sense of Worthlessness	47	17.7

socio-demographic (age, education level, gender) and various types of symptoms were independent variables (Adjusted R-squared: 0.488). Female gender and lower education level as socio-demographic variables, visual problems and myalgia as persistent symptoms were identified as risk factors for lower HRQoL in the robust standard error regression model. The robust standard error regression model is presented with details in Table 3.

Table 2. T-test results: HRQoL difference between symptomatic and non-symptomatic patients.

Symptoms	t	df	p value
Headache*	-2.409	17.386	0.027
Fatigue*	-4.484	60.864	0.000
Dyspnea*	-3.376	26.214	0.002
Hyposmia*	-2.454	29.766	0.020
Loss of Taste	-1.916	18.540	0.071
Dizziness*	-3.749	15.238	0.002
Numbness on Extremities*	-3.770	12.207	0.003
Asthenia*	-4.552	39.667	0.000
Myalgia*	-4.794	36.165	0.000
Visual Problems*	-4.487	8.115	0.002
Hearing Loss	-1.022	3.011	0.382
Hypokinesia*	-3.902	24.110	0.001
Tremor*	-3.129	7.080	0.016
Insomnia*	-2.561	24.278	0.017
Pre-syncope / Syncope*#	-3.018	264	0.003
Amnesia*	-2.965	67.925	0.004
Problem. Difficulty in Concentrating*	-2.321	39.319	0.026
Anxiety*	-3.232	43.719	0.002
Sense of Worthlessness*	-4.167	52.306	0.000

t-test results of "equal variances not assumed" reported except #; *: p value<0.05

Table 3. Robust standard error regression.

Independent Variable	B	Robust Se	t	p value	95% Confidence Interval	
					Lower	Upper
Intercept	0.889	0.053	16.729	0.000	0.784	0.993
Age	0.000	0.001	-0.322	0.748	-0.002	0.002
Education Level*	0.021	0.006	3.274	0.001	0.008	0.033
Gender* (reference: male)	-0.043	0.018	-2,354	0.019	-0.079	-0.007
Headache#	-0.095	0.053	-1.806	0.072	-0.199	0.009
Fatigue#	-0.015	0.027	-0.544	0.587	-0.068	0.039
Dyspnea#	-0.019	0.039	-0.469	0.640	-0.096	0.059
Hyposmia#	0.000	0.077	0.003	0.998	-0.151	0.151
Loss of Taste#	-0.048	0.086	-0.552	0.582	-0.218	0.122
Dizziness#	-0.093	0.077	-1.205	0.230	-0.245	0.059
Numbness on Extremities#	-0.079	0.074	-1.073	0.284	-0.224	0.066
Asthenia#	-0.059	0.040	-1.459	0.146	-0.139	0.021
Myalgia*#	-0.280	0.093	-3.002	0.003	-0.464	-0.096
Visual Problems*#	-0.081	0.032	-2.485	0.014	-0.145	-0.017
Hearing Loss#	0.053	0.132	0.403	0.687	-0.207	0.314
Hypokinesia#	0.030	0.050	0.604	0.546	-0.068	0.129
Tremor#	0.068	0.091	0.744	0.458	-0.112	0.247
Insomnia#	0.030	0.040	0.747	0.456	-0.049	0.110
Pre-syncope / Syncope#	-0.339	0.346	-0.979	0.329	-1.020	0.343
Amnesia#	0.006	0.031	0.191	0.849	-0.055	0.067
Difficulty in concentration #	0.045	0.033	1.357	0.176	-0.021	0.111
Anxiety#	-0.027	0.044	-0.607	0.544	-0.112	0.059
Sense of Worthlessness#	-0.036	0.034	-1.064	0.289	-0.103	0.031

*: p<0,05; #: Reference category: Patients do not have the specified symptom

Discussion

In this study, it was shown that for Long COVID-19 patients, female gender, lower educational level (socio-demographic factors) and visual problems, myalgia (as persistent symptoms) were associated with lower HRQoL, while headache, fatigue, dyspnea, hyposmia, loss of taste, dizziness, numbness on extremities, asthenia, hearing loss, hypokinesia, tremor, insomnia, pre-syncope/syncope, amnesia, difficulty in concentrating, anxiety and sense of worthlessness were not associated. Female gender has been s shown to be associated with lower levels of HRQoL in Long COVID-19 in a previous study [10] as in our study. Fatigue [11], hyposmia [12], dyspnea on exertion, myalgia, asthenia, and arthralgia [13] were also associated with lower levels of HRQoL in the literature. But fatigue, hyposmia, dyspnea were determined as not associated with HRQoL in this study. In the literature, specific symptoms were associated with lower HRQoL by univariate analysis. Univariate analysis causes inflated Type 1 error, so associations can be determined in contrast to reality. In this study multiple analysis was used, so, Type 1 errors were minimalized by removing the confounding effect of symptoms on each other. Even our univariate analysis showed that most of the symptoms were associated with lower levels of HRQoL (Table 2), while multiple analysis showed that only two of the symptoms (visual problems and myalgia) were associated with HRQoL (Table 3). Also, in the previous widest study, dyspnea on exertion, myalgia, asthenia, and arthralgia were associated with decrease in HRQoL of Long COVID-19 patients, but in the study, only patients who had been admitted to ICU were sampled [13]. Meanwhile, in our study, there were no patients requiring hospitalization in ICU. Thus, symptoms associated with HRQoL in different studies may be a result of different characteristics of samples (time from positive RT-PCR result, ICU admission rate, variant of pathogen).

Robust standard error multiple regression is the most precious strength of the study because it allows us to make an inference with minimal Type 1 error. Also, the sample size was almost twice the calculated size, so Type 2 error was expected to be minimal for the study. The results of the study should be generalized with caution because it was conducted in the tertiary hospital. None of the participants of this study required ICU admission, so this may limit inferences from this study for all Long COVID-19 patients. Further studies may be needed to reveal a better understanding of the association between persistent symptoms and lower levels of HRQoL. Also, investigating which interventions aim to redound HRQoL of Long COVID-19 patients, especially those with visual problems and/or myalgia, may be beneficial.

Conclusion

Long Covid-19 patients experience lower levels of HRQoL, especially those who have visual problems and/or myalgia. Interventions to raise the HRQoL of Long COVID-19 patients

should first target visual problems and myalgia.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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